

## CRITICAL REVIEW: BISMUTH AND ITS ADMINISTRATION IN SYPHILIS

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No attempt is made in this paper critically to review the whole of the literature appertaining to the therapeutic use of bismuth in syphilis. It is, however, essential—if a clear conception is to be formed of its value, limitations, and general employment—to understand its mode of action in the body and upon the *treponema pallidum*.

Of late, chemical manufacturers have vied one with another in pouring upon the market a flood of bismuth preparations. They may be conveniently classified as follows :—

- (1) Insoluble preparations in aqueous suspension.
  - (a) Bismuth hydroxide—Spirillan.
  - (b) Colloidal bismuth.
  - (c) Metallic bismuth—Bismostab.
- (2) Insoluble preparations in oily suspension.
  - (a) Tartaro-bismuthates—Trepol.
  - (b) Iodo-bismuthates—Biquinyl.
  - (c) Oxides of bismuth—Muthanol.
- (3) Soluble preparations.
  - (a) Soluble tartaro-bismuthates—Luatol.
  - (b) Bismuth cacodylate—Cytarsan.
  - (c) Diethylene - diamino - gallate of bismuth—Galismuth.

Levaditi has demonstrated a general law with reference to the members of the nitrogen family of elements, *i.e.* those occupying Group V. of Mendelieff's periodic series—arsenic, antimony, vanadium, bismuth, etc.—namely, that they, their compounds or salts, only exhibit their parasiticidal properties after they have been acted upon by the tissues. The blood serum of an animal, into whom sodium-potassium tartaro-bismuthate has been injected intravenously in curative doses, does not exhibit any treponemical action. This shows that the antisypilitic power

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of that salt of bismuth is not dependent upon anything derived from the blood. The salt itself in simple solution is innocuous to the *treponema pallidum*. If, however, there be added to the simple solution fresh extract of liver, the solution becomes actively treponemicidal. This law applies to all the members of Group V. of the Mendeleeff series. In this is to be found the explanation for the superior therapeutic results obtained by intramuscular over intravenous administration of arsenobenzol. Arsenic, antimony, vanadium, and bismuth are alike in the fact that while their parasitocidal power in simple solution *in vitro* is zero, they do, when combined with cellular extracts, exert a specially destructive action upon protozoal organisms.

In the case of bismuth, the action of the cellular extract gives rise to a new compound, "bismoxyl," and it is this which possesses the destructive power against the *treponema pallidum*. The substance in the extract which has the property of changing bismuth into bismoxyl is conveniently termed "bismogene."

Bismoxyl is a bismuth toxalbumin in all respects similar to those arising from arsenic, vanadium, or antimony. Blood appears to be one of the few tissues incapable of producing bismogene wherewith to activate the element into bismoxyl. The activity of the other tissues in this respect varies; for example, bismoxyl produced from brain extract is 1,000 times more potent than that produced by bismogene derived from muscle.

It is not necessary, nor even desirable, that the bismuth be in the form of a chemical compound in order that bismoxyl may be produced. Metallic bismuth, finely subdivided, is more suitable. From experimental evidence it would appear that bismuth compounds must be reduced to elemental bismuth before bismogene can act and give rise to bismoxyl. Levaditi has obtained complete cure of experimental rabbit syphilis by a single intramuscular injection of 0.000317 gramme of bismuth per kilogramme of body weight. This is an almost infinitesimal quantity of the metal, and it is therefore clear that the reactivation of bismuth by bismogene results in a most remarkable transformation of an inert substance into one of high therapeutic value.

It is probable that in the very near future bismoxyl itself will be administered to the patient instead of, as at

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present, requiring his own tissues to manufacture it from the metal or its compounds. Some work has already been done along these lines with satisfactory results.

From a consideration of the foregoing, one is enabled to come to some general, and a few particular, conclusions. Practical experience has shown that the soluble salts possess certain disadvantages. On account of their rapid absorption they are liable to cause certain toxic effects ; and, owing to their equally rapid elimination, their therapeutic value is diminished. With them stomatitis, nephritis, and painful nodosities at the site of injection, are apt to occur. The insoluble preparations suspended in oil are practically painless, but the rate of absorption is slow. The metallic bismuth in very fine subdivision is painless, the rate of absorption is satisfactory, nodosities are rare, as, likewise, are any untoward effects of a toxic character. Moreover, since reduced bismuth is necessary for the production of bismoxyl, this is clearly the most scientific form in which to administer the element. The injection of metallic bismuth, rather than one of its compounds, is a stage nearer to the giving of already-prepared bismoxyl. It is borne out by practical experience that the results are better and are more quickly obtained with metallic bismuth than with any other preparation.

The preparation which has been found most satisfactory and which has been taken into routine use, is *bismostab*. This consists of finely subdivided metallic bismuth suspended in a 5 per cent. glucose solution. The therapeutic action of any bismuth compound varies directly with the actual bismuth content, and it is therefore clear that a compound of low molecular weight is better than one of high molecular weight and a consequently low content of the element ; for example, bismuth subgallate has a higher molecular weight but a lower bismuth content than bismuth oxide. From a theoretical point of view it appears that a suspension of bismuth metal would be ideal ; and this has been borne out by the work of Levaditi, and by general clinical experience.

It might be useful to mention here that some of the manufacturers' descriptions as to the percentage of bismuth present in their preparations are apt to be a little misleading. Where a preparation is stated to contain 97 per cent. of bismuth, this really means that it consists

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of a 10 per cent. suspension of the metal. The metallic bismuth present in bismostab is 99 per cent. of the pure element.

Bismostab is administered by the intramuscular route. The site selected is in the area situated not more than two inches above the outer third of a horizontal line extending from the upper extremity of the internatal furrow, outwards over the buttock. This region is comparatively free from large vessels and nerves.

The patient lies face downwards on the couch, with both buttocks exposed. The injection area is identified, and is painted with tincture of iodine. A sterile intramuscular needle—20-wire gauge and  $1\frac{3}{4}$  inch long—is thrust deeply into the muscle in a perpendicular direction, with a quick stabbing movement. If the point of the needle strikes bone, it must be withdrawn for a quarter of an inch, the object being to place the bismostab deeply into the gluteus medius muscle. When the needle is in position the base must be examined to see if any blood appears. If this occurs, it shows that the bevel is actually within the lumen of a vessel. The needle must then be removed and a fresh one inserted in a slightly different position. It is good practice to defer filling the syringe with the bismostab until the injection needle is in position; in this way, if a vein has been entered, sufficient time will have elapsed during the filling of the syringe, for the blood to appear, and thus enable one to avoid the grave danger of injecting metallic bismuth into the blood stream.

Bismostab is put out in a 5 c.c. vial which must be vigorously shaken before withdrawing any of the contents into the syringe. Owing to the weight of the suspended metal, it begins to settle down almost immediately, so that it is essential that the syringe be filled at once. Unless this is attended to, the last dose withdrawn from the vial will contain much more bismuth than the first. The technique adopted is to thrust the filling needle through the rubber cap, agitate vigorously for a few moments, and at once withdraw the dose into the syringe with the vial held upside down.

The syringe is attached to the needle in the buttock, and the injection is made slowly. With the injection needle still *in situ*, the syringe is detached, the piston is withdrawn to the 1 c.c. mark, and this amount of air is injected to clear the needle. The object of this is to avoid

leaving a track of bismuth along the path of the needle. Failure to observe this rule is one of the commonest causes of pain and suppuration. During the whole procedure the injection needle must be held perfectly steady so as to avoid perforating a vessel. The skin is now pinched up in the form of a cone by the fingers of the left hand—with the point of entry of the needle as the apex—and the needle and syringe together are withdrawn rapidly. The area is gently massaged for a little, the puncture sealed with collodion, and the patient remains in the prone position for a few minutes before dressing.

Experience has shown that the few complaints of discomfort or pain at the site of injection have occurred on cold days, and since adopting the method of warming the bismostab to body heat by placing the vial in warm water before injection, these complaints have ceased.

The soluble compounds of bismuth are more toxic than those which are insoluble; and their toxicity is ten times greater when they are administered intravenously than when injected into the muscles. Symptoms of poisoning have occurred after the application of bismuth subnitrate to superficial lesions such as burns, there being formed a soluble albuminate. Ever since one has worked exclusively with metallic bismuth one's experience of untoward effects has been practically *nil*. Twice has stomatitis occurred, and in each instance was the patient suffering from well marked pyorrhœa. In the Services, where the dental care of the men is now so admirably supervised, one understands that bismuth stomatitis and gingivitis are exceedingly rare. An originally unhealthy condition of the mouth is the main cause of buccal trouble during a course of bismuth injections. If at the same time one of the soluble preparations is being used, the likelihood of stomatitis occurring is very greatly increased. While renal complications were not infrequently encountered when working with the soluble tartaro-bismuthates, the use of bismostab has resulted in their complete disappearance. The asthenia described by the French has not been met with, but it would appear to be of the same character as that which sometimes happens during the use of mercury. The remedy is smaller doses given at longer intervals.

The only absolute contra-indication to the use of bismuth is an unhealthy condition of the patient's mouth. In all cases a careful examination should be made of the

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buccal cavity, and necessary dental treatment must be insisted upon before commencing the injections. Even after that has been done—and in every patient, no matter how clean the mouth may be—special attention must be paid to oral hygiene during the whole course.

In cases of albuminuria which are not the result of a syphilitic nephritis, considerable care must be exercised during bismuth treatment. One does not consider a moderate degree of albuminuria to be an absolute contra-indication; by careful observation, by reduction of the dose, and by lengthening the interval between injections, a considerable amount of bismuth may be administered without ill effect.

Bismuth is indicated in every case and stage of syphilis. Arsenic still undoubtedly holds the premier place, and it should, unless there is some strong reason to the contrary, invariably be used to commence with. This is specially important in those cases which are first seen when syphilitic lesions are present in the mouth.

One's routine treatment in a case of early primary syphilis is :—

Stabilarsan once weekly for	.	8 weeks.
Bismostab thrice weekly for	.	4 „
Stabilarsan once weekly for	.	8 „
Bismostab thrice weekly for	.	4 „
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Total	.	24 „
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Reliance is chiefly placed upon arsenic for rapidity of action in the healing of superficial lesions. The bismuth injections serve not merely as a rest from the arsenic, but they constitute a new and powerful antisymphilitic weapon, which, when they are spread over a period of four weeks, allows the patient to be brought thoroughly under the influence of the drug without causing any trouble or discomfort. By the time that the next eight intravenous injections of stabilarsan are completed, the first bismuth series has been absorbed, and the patient is ready for another bismuthic bombardment.

A point that one conceives to be of not a little importance is that the two remedies should not be given concurrently. One held the same view with regard to arsenic and mercury. There is a very real danger, when giving

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two such antisyphilitic drugs together, of raising the resistance of the *treponema pallidum* to both, and of causing that condition of a persistently positive Wassermann reaction. By alternating bouts of arsenic and bismuth the organism is given no opportunity of developing an immunity to either. No sooner has it commenced to "dig itself in" from the shrapnel of arsenic, than it is driven out into the open by the high explosive of bismuth. It is in this respect worthy of note that Levaditi has found it impossible to raise the resistance of the *treponema pallidum* to bismuth as can be done to arsenic.

It will be observed that mercury is not used. One's opinion is that mercury has become obsolete in the routine treatment of syphilis. One might express the relative values of the antisyphilitic triad as follows:—

Arsenic	.	.	.	.	10
Bismuth	.	.	.	.	8
Mercury	.	.	.	.	3

It is moreover probable that if one considers the arsenic as being given intravenously, another unit might be added to the value assigned to bismuth.

With the introduction of bismuth into the treatment of syphilis, we are now in a position to deal with Wassermann-fast cases. Hitherto, those patients who have had innumerable arsenical and mercurial injections, who present no clinical signs, but whose blood is persistently positive, have been in a most unenviable position. Up to date, one has dealt with a series of nearly a hundred such. They have been treated with bismuth alone, and the results have been excellent. In all, negative results have been secured in the blood, though five still show pathological changes in the cerebro-spinal fluid.

In patients who exhibit an intolerance to arsenobenzol, bismuth is invaluable. Bismuth and mercury are given in alternate courses, but since both are given intramuscularly, it is necessary to have "rest" intervals of from two to four weeks to allow the glutei to recover and the drugs to be absorbed. In one series, patients unable to tolerate arsenic were treated with bismuth alone. In these the bismostab was alternated with iodo-bismuthate of quinine. In all, negative serological results were obtained in nine months, and none have relapsed.

Bismuth is very well borne by infants and children. It

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has a very high value in syphilis of the central nervous system. Specimens of cerebro-spinal fluid have been examined after the injection of large doses of bismuth, but no trace was found, although the method adopted was accurate to four parts per million. It is quite conceivable that bismoxyl may become fixed in the tissues supplied by the cerebral vessels, and that, since the choroid plexus is a secreting gland, and not merely a filter, it may not allow the drug to pass through it.

In interstitial keratitis the results with bismuth have been much better than those obtained hitherto.

### SUMMARY

Bismuth is a most valuable and powerful drug in the therapy of syphilis, in all stages of the disease. It falls very little short of arsenobenzol in its effect upon the superficial and visceral manifestations, and upon the serological reactions of the blood and cerebro-spinal fluid. Unlike arsenic, its use does not expose the patient to any serious risk ; no fatality from its use has been recorded. Having a tremendously higher therapeutic value than mercury, the amount of treatment now required is correspondingly decreased. With bismuth, modern and rapid treatment can be administered to the arsenic-intolerant patient which until its introduction was impossible. Bismuth provides a means of dealing adequately with the Wassermann-fast patient and of securing a permanent negative.

There can be no question but that metallic bismuth is the preparation of choice, not only from the point of view of avoiding toxic effects, but also on account of the mode of action of the element within the body. Finally, emphasis cannot be laid too strongly upon the absolute necessity which exists for a good technique in administration if one would avoid pain, discomfort, and the danger of injecting into the blood-stream.

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